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| 10/782,040 | 02/19/2004 | Tsugunori Notomi | 201487/1024 (E2-001PCT-US | 5624 |

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| EXAMINER | |
|---|---|
| BABIC, CHRISTOPHER M | |
| ART UNIT | PAPER NUMBER |
| 1637 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/782,040 | NOTOMI ET AL. | |
| | Examiner | Art Unit | |
| | Christopher M. Babic | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *54-59* is/are pending in the application.

4a) Of the above claim(s) *20 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 November 2006 and 19 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election of group II, claim(s) 54-59 in the reply filed on November 8, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim(s) 20 and 22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

### *Claim Interpretation*

It is initially noted that, absent any formal structural definition of the phrases --a 3' terminal sequence--, --a 5' terminal nucleotide sequence--, and --an arbitrary region-- they are open to multiple different interpretations that are of critical importance to the prosecution of the instant application.

The only limiting definition provided for the above phrases occurs within the claim(s) themselves; in the case of --a 3' terminal sequence--, the claim requires that the nucleotide sequence, in addition to occurring at the end of the 3' terminus, must anneal to the sample nucleic acid and serve as the origin or nucleic acid synthesis; in the case of --a 5' terminal nucleotide sequence--, the claim requires that the nucleotide sequence, in addition to occurring at the end of the 5' terminus, must be complementary

to an arbitrary region of the first synthesized nucleic acid sequence; and, in the case of --an arbitrary region--, the claim requires that the nucleotide sequence be complementary to a sequence of the first or second synthesized nucleic acid molecule. It is stressed that neither the claim nor the specification requires the nucleotide sequence encompass by the above phrase **to be of a certain length**. Thus, a sequence of a *single nucleotide* meeting the structural limitations outlined above, would anticipate the above claim language. This particular interpretation has certain implications with regard to the prior art applied below (see sections 35 USC 102 and 103 below).

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

**Claim(s) 54-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Claim(s) 54-59 are indefinite because the metes and bounds of the phrase --outside of a region between the region, etc.- is unclear, i.e. it cannot be determined if the primer must anneal outside a region defined by the outer nucleotides of the primers or the outer nucleotides of the region in between the primers.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

**Claim(s) 54, 58, and 59 are rejected under 35 U.S.C. 102(b) as being anticipated by Cleuziat et al. (WO 95/03426 A2; 2 February 1995; 02.02.95) as evidenced by the English translation provided in Cleuziat et al. (U.S. 5,849,547).**

With regard to claim(s) 54, Cleuziat teaches a method (fig. 3; col. 9-15, for example) comprising: A) mixing the following components 1) to 3) with sample nucleic acid as a template (fig. 3; col. 9, line 45-col. 10, line 40, for example) 1) a primer set consisting of four distinct oligonucleotide primers, wherein: the first oligonucleotide primer comprises (i) a 3' terminal nucleotide sequence that anneals to a sample single-stranded nucleic acid molecule and serves as the origin of synthesis for synthesizing a first single-stranded nucleic acid molecule complementary at least in part to the sample single-stranded nucleic acid molecule and (ii) a 5' terminal nucleotide sequence that is complementary to an arbitrary region of the first single-stranded nucleic acid molecule (fig. 3, primer A, for example); the second oligonucleotide primer comprises (i) a 3' terminal nucleotide sequence that anneals to the first single-stranded nucleic acid

molecule prepared using the first oligonucleotide primer and serves as the origin of synthesis for synthesizing a second single-stranded nucleic acid molecule complementary at least in part to the first single- stranded nucleic acid molecule, and (ii) a 5' terminal nucleotide sequence that is complementary to an arbitrary region of the second single-stranded nucleic acid molecule (fig. 3, primer B @ II, for example); the third oligonucleotide primer comprises a nucleotide sequence which anneals to a region of the sample single-stranded nucleic acid molecule, wherein said region is located 3' to a region where the first oligonucleotide primer anneals and outside of a region between (a) the region where the first oligonucleotide primer anneals and (b) a region consisting of a nucleotide sequence identical to the 3' terminal nucleotide sequence of the second oligonucleotide primer (fig. 3, primer G, for example); and the fourth oligonucleotide primer comprises a nucleotide sequence which anneals to a region of the first single-stranded nucleic acid molecule, wherein said region is located 3' to a region where the second oligonucleotide primer anneal and outside of a region between (c) the region where the second oligonucleotide primer anneals and (d) a region consisting of the 3' terminal nucleotide sequence of the first oligonucleotide primer (fig. 3, primer H @ II, for example); 2) a DNA polymerase having strand displacement activity (col. 9, line 45-col. 10, line 40, for example); and 3) one or more nucleotides which are used by the DNA polymerase to extend the primers (col. 9, line 45-col. 10, line 40, for example); and B) incubating the mixture at such a temperature that the nucleotide sequence constituting the first and third oligonucleotide primers can form stable base with the template (col. 9, line 45-col. 10, line 40, for example).

As discussed above, neither the claim nor the specification requires the nucleotide sequence encompassed by the phrases --a 3' terminal sequence--, --a 5' terminal nucleotide sequence--, and --an arbitrary region--, **to be of a certain length**. Thus, a sequence of a *single nucleotide* meeting the structural limitations outlined above, anticipates the above claim language. Figure 3 of Cleuziat shows that amplification of double-stranded nucleic acid, and SEQ ID NO: 1 is an example of a nucleotide sequence that can be amplified within the cited methods. It is implicit to the amplification of the double-stranded form of a sequence, such as SEQ ID NO: 1, within the methods of Cleuziat, that: 1) Primer A has a 5' terminal nucleotide sequence that is complementary to an arbitrary region of the first single-stranded nucleic acid molecule, i.e. primer A contains **a single nucleotide** at its 5' end that is complementary to an arbitrary nucleotide (region) of the first synthesized molecule; 2) Primer B has a 5' terminal nucleotide sequence that is complementary to an arbitrary region of the second single-stranded nucleic acid molecule, i.e. primer B contains **a single nucleotide** at its 5' end that is complementary to an arbitrary nucleotide (region) of the second synthesized molecule; 3) Primer G anneals and outside of a region between (a) the region where the first oligonucleotide primer anneals and (b) a region consisting of a nucleotide sequence identical to the 3' terminal nucleotide sequence of the second oligonucleotide primer, i.e. primer G anneals outside a region between (a) the region where primer A anneals and (b) **a single nucleotide** identical to the nucleotide present at the 3' terminal end of Primer B; and 4) Primer H anneals and outside of a region between (a) the region where the second oligonucleotide primer anneals and (b) a

region consisting of a nucleotide sequence identical to the 3' terminal nucleotide sequence of the first oligonucleotide primer, i.e. primer H anneals outside a region between (a) the region where primer B anneals and (b) **a single nucleotide** identical to the nucleotide present at the 3' terminal end of Primer A. Thus, the claimed invention is anticipated.

With regard to claim(s) 58, Cleuziat teaches a detector for detection of products (col. 27, lines 35-55, UV detection, for example).

With regard to claim(s) 59, Cleuziat teaches reverse transcription of RNA (col. 20, lines 45-65, for example).

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**Claim(s) 55-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cleuziat et al. (WO 95/03426 A2; 2 February 1995; 02.02.95) as evidenced by the English translation provided in Cleuziat et al. (U.S. 5,849,547) as applied to claim(s) 54, 58, and 59 above, and further in view of Bloch (U.S. 5,972,618).**

With regard to claim(s) 55-57, the methods of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach the use of melting temperature regulators.

It is submitted that melting temperature regulators, i.e. Betaine, were well known in the art at the time the claimed invention was made as taught by Bloch. Bloch teaches high concentrations of Betaine (col. 12, lines 40-63, 2-3M, for example) are preferred PCR sensitivity enhancers because it improves polymerase-template interaction without enzyme inhibition (col. 4, lines 49-60, for example).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to add Betaine to the polymerase reactions of Cleuziat for the expected benefit of improved polymerase-template interaction without enzyme inhibition as taught by Bloch.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

It is noted that only representative claims will be discussed.

**1. Claim(s) 54 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim(s) 5, 12, and 13 of Notomi et al. (U.S. Patent No. 6,410,278 B1) (Notomi I).**

Although the conflicting claims are not identical, they are not patentably distinct from each other because they are all drawn to the same general inventive nucleic acid amplification procedure. For example, steps A3 and A6 within claim 5 of Notomi I do not expressly recite the use of the third and fourth primers as recited in claim 54 of the instant invention, however, it would have been *prima facie* obvious to one of ordinary

skill in the art at the time of invention to incorporate primers third and fourth primers as structurally described in claim 54 of the instant invention to "displace" a newly synthesized nucleic acid molecule as described steps A3 and A6 within claim 5 of Notomi, thus arriving at the claimed invention.

**2. Claim(s) 54 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim(s) 3, 4, 27, and 28 of Notomi et al. (U.S. Patent No. 6,974,670 B2) (Notomi II).**

Although the conflicting claims are not identical, they are not patentably distinct from each other because they are all drawn to the same general inventive nucleic acid amplification procedure. For example, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to incorporate the fourth primer as structurally described in claim 54 of the instant invention within the methods as recited in claim 3 to "displace" a newly synthesized second-single stranded nucleic acid molecule as described within claim 1 of Notomi (see claim 4 of Notomi II), thus arriving at the claimed invention.

***Conclusion***

**Claims 54-59 are rejected. No claims are allowed.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 571-272-8507. The examiner can normally be reached on Monday-Friday 7:00AM to 4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

1/23/06

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1/23/07